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LOW PRESSURE HYPERBARIC OXYGEN THERAPY FOR PEDIATRIC BRAIN INJURY, A MINIMAL RISK MEDICAL TREATMENT RESPONSE TO NUTHALL ARTICLE

Dear Sirs:

We read the recent contribution to your esteemed journal by Nuthall, et al with extreme disappointment. Unfortunately, this article distorts the true complication rate of low-pressure hyperbaric oxygen therapy (LPHBOT) in the treatment of pediatric neurological conditions. Noticeably missing from the paper is an estimate of the frequency with which these complications occur. Without such perspective, this article misleads the medical community and fuels the unfounded fear that LPHBOT is dangerous for children with cerebral palsy, when in fact it is both safe and an extremely useful adjunctive therapy.

The first case mentioned in the article, vomiting with aspiration, is a complication that can occur in an adult or pediatric patient with gastro esophageal reflux in many medical settings, hyperbaric or normobaric. Unfortunately, the article does not give enough information for a critical appraisal of the patient's care. Air swallowing at anytime, but especially during and HBO treatment, can lead to gastric distention, which can worsen, on ascent. It is easily avoided by simple venting in patients with feeding tubes. The "tight-fitting" oxygen hood implies neck constriction, but the hood used in multiplace chambers throughout the United States and Canada in fact utilizes a comfortably fitting latex neck dam. A competent attendant can easily remove the hood if needed and suction should be available in the chamber. Aspiration is a rare complication of HBOT, but does occur in the ill adult population. To put the matter in perspective in the pediatric population, since the first HBOT for a CP child in North America in 1992 (2) authors PGH and RAN have logged over 35,000 treatments on brain-injured children without a single case of primary aspiration or air embolism. Approximately 7,000 of these treatments were performed on an IRB-approved protocol. The point is that this case report represents a very rare indeed, and most likely a completely avoidable one in a setting of adequate care. We believe the slight risk is acceptable given the positive responses in the vast majority children treated.

The second case is an unfortunate example of an acutely ill child who should have been denied treatment by proper pre-treatment evaluation the day of the accident. The authors attribute the child's cerebral infarct to an oxygen embolism caused by primary arterial bubbles during decompression or venous oxygen bubbles breaching the pulmonary filter or a patent foramen ovale (PFO). In our opinion, this diagnosis is exceedingly unlikely, the mechanisms suggested by the authors nearly impossible to account for their diagnosis, and their argument not supported by the references cited. Primary arterial bubbles of any gas are only seen in explosive decompressions (3). No such scenario is described in the article.

Primary venous bubbles occur in almost all decompressions, but oxygen decompression sickness, and presumably bubbles, have only been documented in animals at 3.53 atmospheres absolute (ATA) of oxygen (4) which is over two times the oxygen exposure of this patient. Furthermore, venous bubbles of any gas will form in proportion to the gas load of the dive. This patient's dive, 1.5 ATA, is a very shallow exposure, which would produce minimal, or no bubbles. Venous bubbles that do form during decompression have been measured to be mostly 19 to 180 microns with some larger bubbles up to 700 microns (5). While it is possible for the bubbles to breach insulated lungs (Para influenza induced respiratory failure) or proceed through a PFO to cause an infarct they would have to selectively coalesce and be retained in the much larger MCA. This is highly unlikely, given the argument above and the fact that oxygen bubbles should be readily metabolized, and hence transient.

Lastly, the two references cited to justify two of the proposed mechanisms don't apply this case; both are articles on iatrogenic air embolism (6, 7) and/or pulmonary barotrauma (6). In addition, the Muth article (6) contradicts the authors' mechanisms by stating, "Cerebral arterial gas embolization typically involves the migration of gas to small arteries (average diameter, 30 to 60 microns)." The MCA is much larger in a 10-month-old child. Muth further states that all

patients with clinical symptoms of arterial gas embolism should receive recompression treatment with hyperbaric oxygen. To attribute this child's cerebral infarct to an oxygen embolism by any mechanism is nearly impossible. More likely, this infarct was the result of a vasospastic event, fat embolism from infected marrow, or some other etiology related to the child's concurrent infection.

Patient safety is paramount and we believe that physician attended HBOT is mandatory.

The Nuthall article begs the greater question of why patients are driven to non-physician attended facilities to obtain medical treatment. The British Columbia College of Physicians and Surgeons (8) and an ex-president of the Undersea and Hyperbaric Medical Society (UHMS) purportedly speaking for the UHMS (9) have now forbidden and threatened doctors, respectively, should they treat non-UHMS approved pediatric neurological disease with HBOT. This is a dangerous and intolerable precedent. Off-label use of any FDA approved device or drug by a qualified ethical physician constitutes the legal practice of medicine. It is to the medical professions embarrassment that families are forced to seek care from facilities, which may be ill equipped or staffed by personnel who lack medical training.

The call for a randomized controlled trial, while desired, strikes a loud and clear double standard. There exists far more evidence to support cerebral palsy as a UHMS HBOT "accepted indication"(10) than existed for cerebral abscess, the last indication added to the list in 1996. In addition, reviews of the accepted indications list by author PGH in 1998 for a presentation at the Advanced Topics Course in Hyperbaric Medicine (11), by evaluators for the Calgary Regional Health Authority in 1999 (12), and Blue Cross/Blue Shield in 2000 (13) found that as many as 6 -7 of the accepted thirteen diagnoses are not supported by either controlled clinical trials and/or adequate research. The statement by the Nuthall article that neither they nor the UHMS can recommend HBOT for CP in the absence of randomized (Nuthall) controlled (UHMS and Nuthall) clinical trials is inconsistent.

In conclusion, we must correct the Nuthall article's frightening implication and inform the medical community that low-pressure HBOT for pediatric brain injury is a very low risk medical treatment, supported by our combined experience of greater than 35,000 patient treatments.

Thank you,

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2 Cases in Canada

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ELECTRONIC ARTICLE: Hyperbaric Oxygen Therapy for Cerebral Palsy: Two Complications of Treatment. Gabrielle Nuthall, MBChB, FRACP*, Michael Seear, MD, FRCPC*, Michael Lepawsky, MD, FCFP, David Wensley, MBBS, FRCPC*, Peter Skippen, MBBS, FRCPC*, and Juliette Hukin, MBBS, FRCPC§

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ABSTRACT

There is growing interest in the use of hyperbaric oxygen therapy (HBO2) for children with cerebral palsy. Although there is no rigorous evidence to support this management, private hyperbaric centers have been established throughout the United States and Canada. There is likely to be increasing pressure on pediatricians and other health professionals to prescribe HBO2. We describe 2 children with cerebral palsy who suffered significant morbidity immediately after treatment with hyperbaric oxygen. Both the temporal association and pathologic findings suggest that the hyperbaric treatment is likely to have been responsible for the resulting complications. As with any new therapy, we suggest waiting for the results of a randomized, controlled trial before recommending this treatment.

Key words: hyperbaric oxygen, cerebral palsy.

Cerebral palsy (CP) is a nonprogressive disorder of the developing brain affecting the motor system, with a broad clinical spectrum. It can be associated with epilepsy and abnormalities of speech, vision, and intellect. It affects ~2 to 3 per 1000 school-aged children.¹ It was previously believed that CP was the result of medical complications occurring around the time of delivery. However, there is growing evidence that the majority of cases are caused by intrauterine insults or structural abnormalities of the central nervous system.^{1,2}

There is currently no known medical treatment for CP other than supportive care, usually provided by a multidisciplinary team in most pediatric centers. Understandably, some parents look for treatments outside conventional mainstream medicine. There is growing interest in the use of hyperbaric oxygen therapy (HBO2) for children with CP.³⁻⁷ Although there is no scientific data to support the use of this therapy, private hyperbaric centers have been established in Europe and North America principally for the treatment of CP.

Montgomery et al⁷ recently published the results of a pilot study on the treatment of 25 children with spastic diplegic CP with HBO2. Results showed improved gross motor function and fine motor control, reduced spasticity, and improvements noted by the parents. However, this study has a number of limitations, many of which are acknowledged by the authors. It involved a small number of children, there was no control group, and there was no blinding of the therapists performing the assessments.

The treatments were conducted at 2 different hyperbaric centers with different treatment protocols and some of the assessments were of a subjective nature.

During HBO2, the partial pressure of oxygen (PO₂) in the blood is greatly increased by exposing the child to elevated ambient pressures while breathing 100% oxygen. Treatment regimens differ but generally treatments involve pressurization to 1.5 to 2 atmospheres for 60 to 90 minutes. Clients must breathe 100% oxygen. In a multiplace chamber (hyperbaric chamber in which several patients can be treated simultaneously), this is administered through an enclosed vinyl diving hood with neck seals.

Justifications for HBO₂ in CP vary but generally rely on a claim that high tissue oxygen levels can improve the function of damaged cells within the central nervous system.^{4,8,9} There are no controlled trials to support these claims. At least 2 private centers have informative web sites explaining their rationale for treatment.^{8,9}

When used for conventional indications, HBO₂ is generally safe. For treatments <120 minutes and pressures below 3 atmospheres, central nervous system complications occur in 1% to 2% of patients and reversible barotrauma in 15% to 20%.³ We report 2 children with CP who required admission to our pediatric intensive care unit (ICU), each within a few hours of a hyperbaric oxygen treatment. The clinical presentation and close temporal association with HBO₂ suggest that this therapy is likely to have contributed to the complications.

CASE REPORTS

Case 1

A 4-year-old boy with CP was admitted to our pediatric ICU with severe respiratory distress, 2 hours after completing a hyperbaric oxygen treatment. He was the product of a breech presentation and required extensive resuscitation at birth. By 4 years of age, he could stand with support but had no speech and poor comprehension. He required anticonvulsant therapy for a symptomatic seizure disorder. During the day of admission, he received 2 courses of HBO₂; each treatment lasted 90 minutes with 15 minutes for descent and 15 minutes for ascent. The child was dived to 1.75 atmospheres on each occasion. During treatment, his head was completely enclosed by a vinyl hood with latex seals around his neck for delivery of oxygen. Between the 2 treatments he was fed orally. He regurgitated his feed during the second treatment. He subsequently developed increasing respiratory distress that prompted his intensive care admission. He had been well on the morning of the treatments and had no past history of aspiration or choking episodes. His chest radiograph revealed dense opacification of the left lung field compatible with an acute aspiration. He was treated with intravenous antibiotics, intensive chest physiotherapy, and bi-level positive pressure mask ventilation. He was discharged to the ward after 3 days in the ICU. A feeding study subsequently revealed free reflux and tracheal aspiration of feeds.

Case 2

A 10-month-old boy with CP was admitted to our ICU with acute respiratory failure that required immediate intubation and ventilatory support. He also required intravenous anticonvulsants for control of what was observed to be a brief generalized tonic clonic seizure that occurred after positive pressure ventilation was instituted. His medical history was significant for severe perinatal asphyxia after uterine rupture during delivery. This resulted in spastic CP with microcephaly and developmental delay, cortical visual impairment, bulbar dysfunction, and recurrent pneumonia. The child had been receiving twice-daily hyperbaric oxygen treatments for the 2 days before admission. Each treatment involved pressurization to 1.5 atmospheres for 1 hour with 15 minutes to dive and 15 minutes to ascend. HBO₂ treatment was administered in a monoplace chamber, with a parent present, and with ambient oxygen of 100%. There were no obvious complications during treatment. Routine hematology on admission to the ICU revealed a platelet count of $16 \times 10^9/L$ (normal range: $180-140 \times 10^9/L$). A diagnosis of idiopathic thrombocytopenic purpura (ITP) was made, which was believed to be related to the parainfluenza type 3 found on tracheal aspirate. He subsequently had 2 further generalized tonic clonic seizures during the first day of admission. In view of the low platelet count and the ongoing seizure activity, a computed tomography (CT) scan of his head was organized to exclude an acute intracerebral hemorrhage.

A CT scan of his head showed an acute nonhemorrhagic infarction of the left hemisphere thought to be attributable to a thrombus or embolus to the middle cerebral artery. An echocardiogram demonstrated a patent foramen ovale with bi-directional flow. No other embolic events were identified and coagulation studies were normal, no other investigations for a hypercoagulable state were performed. His thrombocytopenia responded rapidly to treatment with intravenous - globulin. In view of this rapid response and the recent association of a number of other children developing ITP in association with parainfluenza type 3, it was believed that a bone marrow aspirate to confirm the diagnosis of ITP was not necessary. He was extubated successfully soon after transfer back to his home state. The only clinical manifestation of the left hemispheric infarction was the onset of seizure activity. There was otherwise no change in his neurological examination.

DISCUSSION

These 2 children with CP suffered significant medical problems shortly after hyperbaric oxygen therapy. We believe that the close temporal relationship between these 2 events, combined with the clinical features of the cases, support the suggestion that HBO₂ is likely to have been responsible for these complications.

In the first case, the child was well on the morning of his admission, did not have a fever, and was subsequently shown to have free gastroesophageal reflux with aspiration. It is likely that he suffered a serious aspiration event during the 90 minutes that his head was completely enclosed within a tight-fitting vinyl hood. Gas buildup in the stomach during

pressurization, either from a recent feed or from air swallowing, will conform to Boyle's law. During ascent from the treatment depth, there will be gas expansion with potential for reflux, aspiration, and vomiting.¹⁰ This may have contributed to this child's aspiration event.

Swallowing disorders and reflux are common among children with CP.¹¹ When planning a treatment regimen for this group of children, consideration of oral feeding, access to the airway, provision of trained personnel, and suction equipment would be a sensible minimum requirement.

Although the second case had a very low platelet count, the CT scan revealed an embolic or thrombotic, rather than a hemorrhagic, stroke. We propose that the most likely mechanism for the middle cerebral artery occlusion was a gas embolism.

It was unlikely to have been an air embolism, but theoretically possible to have been an oxygen embolism. When breathing 100% oxygen at 2 atmospheres, the PO₂ in the arterial blood is >1000 mm Hg. During the 15-minute ascent, this begins to fall, dropping to 100 mm Hg when breathing atmospheric pressure air. Oxygen is not highly soluble in plasma, so it is theoretically possible for bubbles of oxygen to form in the arterial blood during this equilibration period leading to occlusion of the middle cerebral artery.

Two other pathophysiological factors may be considered in accounting for the proposed clinical presentation of a cerebral oxygen embolism. During the decompression phase of treatment, oxygen bubbles might form in the lower pressure venous system and be ejected into the left atrium through the patent foramen ovale. They would then travel through the left atrium into the systemic circulation and might lodge in the left middle cerebral artery. Alternatively bubbles might sequester in the pulmonary arterial bed, ultimately pass through to the pulmonary venous bed, travel to the left atrium and left ventricle, and be ejected to lodge in the left middle cerebral artery. Both these mechanisms have been described in the literature.^{12, 13}

The Undersea and Hyperbaric Medical Society provides a list of conditions for which HBO₂ is an acceptable treatment. CP is not one of these indications. Their recommendation is that HBO₂ should not be used for any other indication except in the context of controlled clinical trials. Although HBO₂ is a relatively safe treatment, it does have documented risks.³ Until the results of a randomized, controlled trial are available, we would suggest that HBO₂ not be recommended as a treatment for CP in children.

FOOTNOTES

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ABBREVIATIONS

CP, cerebral palsy; HBO₂, hyperbaric oxygen therapy; PO₂, pressure of oxygen; ICU, intensive care unit; ITP, idiopathic thrombocytopenia purpura; CT, computed tomography.

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